PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Amjad Ali, et al.		
Serial No.:	10/508,897	Case: 21035YP	Art Unit: 1626
Filed:	April 28, 2005		
For:	1H-BENZO[F]INDAZOL-5-YL DERIVATIVES AS SELECTIVE GLUCOCORTICOID RECEPTOR MODULATORS		Examiner: Freistein, Andrew B.

Commissioner for Patents
Alexandria, VA 22313

DECLARATION OF CHRISTOPHER F. THOMPSON

Sir:

I, Christopher F. Thompson, hereby declare the following:

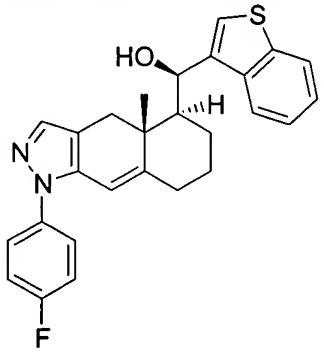
1. I was awarded a Bachelor's degree in chemistry in 1993 by Providence College, Providence, Rhode Island.

2. I was awarded a Ph. D. degree in chemistry in 1999 by Princeton University, Princeton, New Jersey.

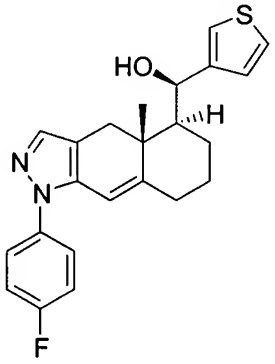
3. I have been employed by Merck & Co., Inc., Rahway, New Jersey continuously since 2001 and currently hold the title of Research Fellow in the Department of Medicinal Chemistry.

4. I am a joint inventor named in the captioned patent application.

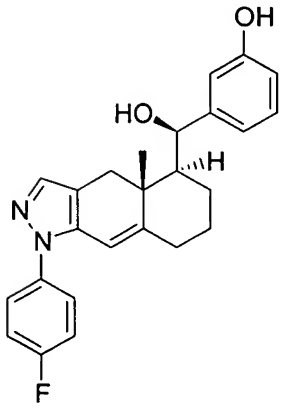
5. While employed at Merck, I synthesized the compounds listed below in the United States. These compounds were included in the instant patent application, Serial No. 10/508,897. Below each compound I have provided the example number in which they are identified in this application. These compounds are specifically claimed in Claim 17 of the instant patent application, Serial No. 10/508,897.



EXAMPLE 39



EXAMPLE 42



EXAMPLE 70

6. The above listed compounds were synthesized by me prior to January 22, 2002 as evidenced by the attached copies of notebook entries made by me that I signed and dated prior to January 22, 2002. The dates have been redacted from the attached notebook entries.

7. I hereby declare that all statements made herein of my own knowledge are true and that all statement made of information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,

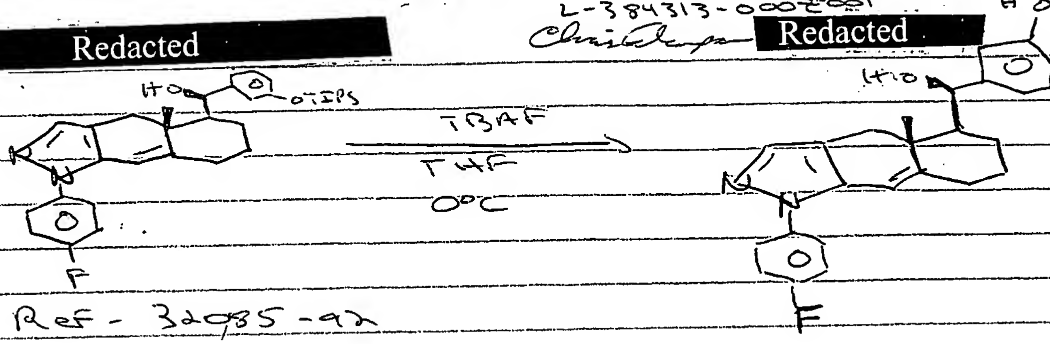
October 18th, 2006
Date

Christopher F. Thompson

[redacted]

This compound was assigned
L-384313-000Z001
Chris Thompson [redacted]

[redacted]



Ref - 32085-92

Materials

Name	equiv.	amt.	mmol	MW	≥	Source
silyl ether	1	7.8mg	0.0139	560		32085-103
(1 M soln in THF) TBAF	5	70uL	0.0696			Aldrich
THF		1mL				Still

The starting compound is dissolved in THF + Cool to 0°C : add TBAF. Rxn. complete after 30 minutes. Dilute w/ EtOAc after adding 50uL of HOAc to quench. Rxn. looks very clean. Wash w/ H_2O, brine, dry over Na_2SO_4, filter + ~~concentrate~~ CT store dilute in fridge.

Chris Thompson [redacted]

[redacted]

Concentrate. Purified by f-c. w/ 50% EA / Hex. Problems w/ solubility. Tried to use some CH_2Cl_2, but it didn't help that much. Product tailed off over many fractions. Compound seems soluble in CH_2Cl_2/MeOH mixture & this would probably be better for handling it in the future.

Chris Thompson [redacted]

[redacted]

Only 2mg here. 1H NMR looks good (DMSO) single compound.

Chris Thompson [redacted]

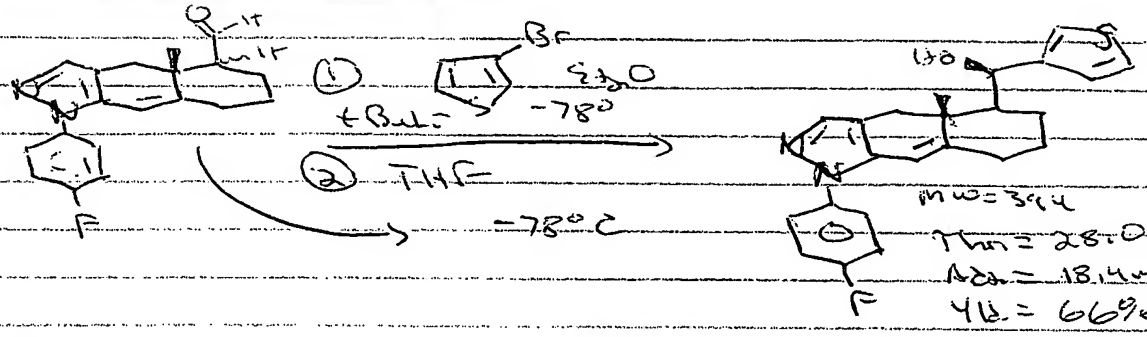
0105

Countersigned

[redacted]

Date

Redacted



Materials

Name	Equiv.	amt.	mmol	mw & Source
3-Bromothiophene	10	65uL	0.71	163.04 #74 Aldrich
(1.7M in pentane) tBuLi	20	840uL	1.42	Aldrich
Et2O		8mL		Aldrich
Aldehyde	1	22.0mg	0.071	310 - 32685-80
THF		2mL		Stock

The 3-bromothiophene was dissolved in Et2O + cooled to -78°C. Add tBuLi Rxn. turns light yellow. Stir 20 min @ -78°C. Cannula in Aldehyde in 2x1mL of THF. Stir 45 min @ -78°C. TLC shows all s.m. consumed 1 major product w/ minor trailing just behind. ~~Dilute~~ Quench w/ IPA, pour into sat'd NH4Cl. Dilute w/ EtOAc. Wash w/ H2O, brine. Dry over Na2SO4, filter + concentrate. Purify on ISCO w/ 5->15% EA/Hex over 35 min. 18.4mg isolated.

Chris Thompson Redacted

Redacted

TLC - 25% EA/Hex PMA stain

1) s.m.
2) co-spot
3) rxn.

1 2 3

'HNMR, LCMS look good

Chris Thompson Redacted CT

Redacted this compound was assigned L-385532-0002001

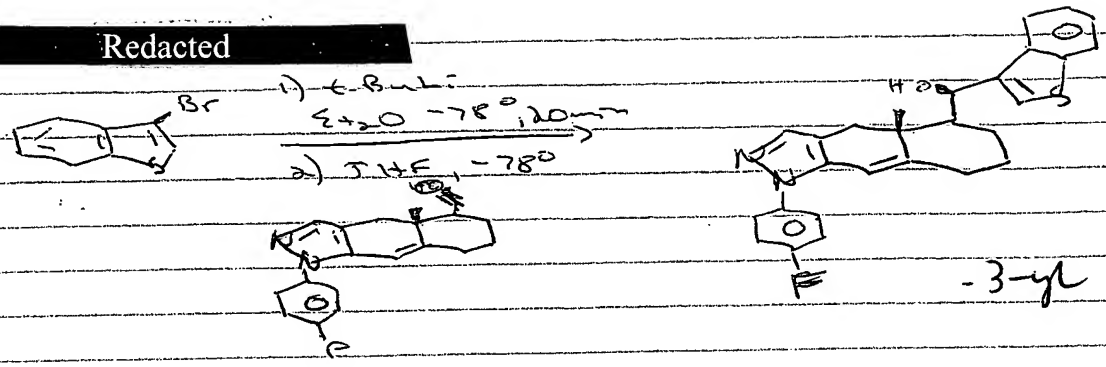
Chris Thompson Redacted

Countersigned

Redacted

Date

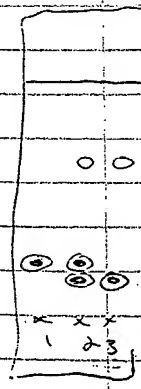
Redacted



Materials

Name	equiv.	amt.	mmol	MW	d	Source
3-Bromo thianaphthene	10	110uL	0.839	~~183.04~~ 213.10	1.629	Aldrich
(1.7M in pentane) t-BuLi	20	986uL	1.68			Aldrich
Et2O		8mL				Aldrich
Aldehyde	1	26.0mg	0.084	310	—	32085-80 St-11
THF		2mL				

The starting bromide was dissolved in Et2O & cooled to -78°C. Add tBuLi & stir @ -78°C for 20 min. Rxn. turns faint yellow, TLC - 25% EA/Hex but very little noticeable color change. PMit stays. Add aldehyde by cannula. Let stir 1) S.M. 45 min @ -78°C. Rxn. complete. 2) compar Quench w IPA @ low temp & then 3) Rm. Pour into sat'd NH4Cl. Dilute w EtOAc. Wash w H2O, brine. Dry over Na2SO4, filter + concentrate. Purify by ISCO 4% -> 20% EA/Hex over 30min. Product peak seems to have shoulders on both sides. Take center cut of fractions. LCMS good, 1H NMR shows 3 compounds in 17:1:1 ratio 23mg. here.



Chris Thompson

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Continued on p. 32085-128

Countersigned

Redacted

Date

128 [redacted]

[redacted]

32085-125 continued

Chiral HPLC was difficult, b/c material kept crashing out of IPA/hexane solutions. Compound is very crystalline from this solvent system, although it is quite soluble in EtOAc : CH_2Cl_2.

Finally a portion was purified by CT reverse chiral HPLC, OD column, 35% IPA/Hexanes, 6.2 mg pure material isolated.

-The rest of the material was stored impure

Chris Thompson [redacted]

[redacted]

^1H NMR looks good. Minor diastereomers removed.

This compound was assigned L-386248-0002001

Chris Thompson ADCT [redacted]

CT

0128

Countersigned

[redacted]

Date

P&T OFFICE ACKNOWLEDGEMENT

ATTORNEY	DATE
Raynard Yuro	10/20/06
CASE NUMBER/	**SERIAL NUMBER**
21035YP	10/508,897

DATE FILED

September 2, 2004

APPLICANT

Amjad Ali, et al.

EXPRESS MAIL NO.

The Patent & Trademark Office acknowledges, and has stamped hereon, the date of the receipt of the items checked below:

- ☐ AMENDMENT
- ☐ APPEAL AND FEE
- ☐ ASSIGNMENT
- ☐ BRIEF
- ☐ CERTIFICATE OF CORRECTION
- ☐ FINAL FEE
- ☐ LETTER
- ☐ REQUEST FOR F.F. LICENSE
- ☐ INFORMATION DISCLOSURE STATEMENT
- ☐ PTO 1449 & REFERENCES
- ☒ PETITION FOR EXTENSION OF TIME & FEE 1 mo.
- ☐ INVITATION TO CORRECT
- ☐ DEMAND-CHAPTER II & FEE SHEET
- X Response to Restriction Requirement
- X Declaration of Christopher F. Thompson

F4424